REMARKS

By this amendment, claims 1, 6, 9-15, and 18 have been amended, claims 20-24 have been added, and claims 2-4 have been cancelled without prejudice. Claims 14-19 stand withdrawn from consideration and thus claims 1, 5-13, and 20-24 are currently pending and under examination in the present application. For the reasons set forth below, Applicants submit that the present amendments and arguments place this application in condition for immediate allowance.

As an initial matter, by the present amendments, claims 1, 6, 9, 10, and 13 have been amended to recite particular combinations that consist essentially of the enkephalinase inhibitors racecadotril or dexecadotril and the antiemetic agents ondansetron or granisetron. Support for these amendments can be found throughout the specification and claims of the present application, as filed. Additionally, these amendments to the claims are believed to be commensurate in scope with the Declaration previously submitted in conjunction with this application, as was suggested by the Examiner during the Interview of November 2, 2009. By the present amendments, claims 20-24 have also been added to present the particular combinations of the enkephalinase inhibitors racecadotril or dexecadotril and the antiemetic agents ondansetron or granisetron in an alternate form. Support for the addition of these claims can be found, for example, on pages 6-7 of the specification of the present application.

In the Office Action dated July 28, 2009, the Examiner initially maintained a rejection of claims 9-12 under 35 U.S.C. §112, second paragraph as being indefinite. In particular, the Examiner asserted that the metes and bounds of the phrase "corresponding

doses according to body weight for children and babies" could not be precisely determined because factors such as modes of administration, body weight, dosage forms, and renal and hepatic status, must be considered when formulating a dosage form. Without addressing the merits of this rejection, the rejection has been rendered moot by virtue of the present amendments, which remove the phrase "corresponding doses according to body weight for children and babies" from claims 9-12. Accordingly, Applicants submit that this rejection is respectfully traversed and should be withdrawn.

In the Office Action, the Examiner then also maintained a rejection of claims 1-19 under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent Application Publication No. 2004/0115258 ("Stroppolo") in view of a reference by Boige, et al. (Bulletin du Cancer). In particular, the Examiner continued to assert that Stroppolo lists categories of drugs, such as antidiarrheals and antiemetics, that may be combined in a formulation, and that, in light of Boige, one of ordinary skill in the art of oncology would have been motivated to select both an antidiarrheal and an antiemetic for a specific patient population. For the reasons set forth below, Applicants submit that this rejection is also respectfully traversed and should be withdrawn.

Contrary to the Examiner's assertions, neither Stroppolo or Boige, alone or in combination, teach or suggest the combination of an antiemetic agent and an enkephalinase inhibitor, much less the specific combination of racecadotril or dexecadotril and granisetron or ondansetron as recited in the claims of the present application, as amended. Stroppolo only describes pharmaceutical compositions that include cyclodextrin in combination with one or more active ingredients. In this regard,

and as pointed out in the previous response in this case, racecadotril and ondansetron are simply included among an exhaustive list of agents in Stroppolo, which basically comprises the entire pharmacopoeia. As the Examiner has acknowledged, there is no teaching or suggestion in Stroppolo whatsoever that would provide a reason for one of ordinary skill in the art to particularly select ondansetron and racecadotril from the exhaustive list of agents and then combine them in the same composition.

Similarly, Boige merely suggests that, on one hand, ondansetron can be used as an antiemetic agent and that, on the other hand, racecadotril can be administered for the treatment of diarrhea in patients receiving chemotherapy. Boige does not teach or suggest a combination of these two drugs, and certainly does not teach or suggest that administering a combination of these two drugs can inhibit the side effects of racecadotril or potentiate the antidiarrheal effects of racecadotril, as described in the present application.

Indeed, the specific combination of racecadotril or dexecadotril and ondansetron or granisetron provides an *in vivo* synergistic effect that is apparent from the experimental results described in the present application, as well as in the Declaration of Dr. Jeanne-Marie Lecomte, which was previously submitted in conjunction with this application pursuant to 37 C.F.R. §1.132. For example, as set forth on pages 13-14 of the specification of the present application, it was observed that racecadotril alone only induces a partial protection at a dose of 40 mg/kg p.o. However, when racecadotril was administered at the same dose with ondansetron, the combination elicited a complete antidiarrheal effect. Similarly, as also set forth on pages 13-14 of the specification, it was

observed that when 0.1 mg/kg of dexecadotril was administered alone, it was only partially protective against diarrhea. When dexecadrotil was administered with ondansetron at 1 mg/kg though, the combination was found to completely prevent the occurrence of diarrhea. These synergistic results would not have been expected by one or ordinary skill in the art with knowledge of each drug alone, much less would they have been expected by a person of ordinary skill in the art upon reviewing the Stroppolo and Boige references cited by the Examiner.

Furthermore, it is also the case that, besides potentiating the antidiarrheal effects of racecadotril and dexecadotril, administering an antiemetic agent, such as granisetron, with an enkephalinase inhibitor, such as racecadotril, can additionally suppress the side effects of the enkephalinase inhibitor. The administration of enkephalinase inhibitors typically results in the undesirable side effect of increasing intestinal transit. As shown in the previously-submitted Declaration of Dr. Jeanne-Marie Lecomte, however, co-administration of racecadotril and granisetron at the same doses not only inhibits the increase in intestinal transit induced by racecadotril, but also decreases the intestinal transit to a level below the control rate. Again, these unexpected results are neither taught nor suggested by the cited Stroppolo or Boige references, alone or in combination.

In summary, by the present amendments, the claims of the present application have been amended to recite combinations that consist essentially of the specific enkephalinase inhibitors racecadotril or dexecadotril and the specific antiemetic agents ondansetron or granisetron. These particular combinations, as well as the surprising and unexpected results that are achieved by their co-administration, are neither taught nor

remotely suggested by the cited Stroppolo and Boige references. Accordingly, Applicants respectfully submit that the present invention, as reflected in the amended claims, is not rendered obvious by the cited references and that the claims of the present application are clearly patentable over those references. Applicants thus submit that the Examiner's rejections on the basis of those references is respectfully traversed and should be withdrawn.

In light of the amendments and arguments provided herewith, Applicants submit that the present application overcomes all prior rejections and objections, and, upon entrance of the present amendments, will be placed in condition for immediate allowance. Such action is respectfully requested.

Respectfully submitted,

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